

In the specification

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At page 1, below the title and above the "Background of the Invention", insert --This is a continuation of U.S. application Ser. No. 08/139,972, <sup>filed October 20, 1993, now abandoned,</sup> which is a divisional of U.S. application Ser. No. 07/956,569, filed on October 5, 1992, issued as U.S. Patent No. 5,278,175, which is a continuation of U.S. application Ser. No. 07/646,564, filed on January 25, 1991, now abandoned.--.

4/18/94

REMARKS

Introduction

Claims 1-6 and 10-29 are pending in the application. Claim 8 has been canceled and claims 26-29 have been added. Claims 20-25 are withdrawn from consideration. Applicants hereby elect to prosecute the claims of Group I (nos. 1-6, 8, 10-19). Since new claims 26-29 fall within the set of Group I claims, applicants submit that these claims are to be prosecuted as well. The specification of the application has been amended herein to indicate prior U.S. applications from which this application claims priority.

Certain claims have been amended and claims 26-29 have been added. Claims 1 and 10 have been narrowed. The group 4-fluorophenyl has been added as an R group to claims 3 and 12. This group finds support at page 2, line 11, of the application. Claim 19 has been amended to delete "unit dosage" as a limitation. The compounds of the present invention can be administered in unit dosage form or otherwise, as indicated at pages 17 and 18 of the application.

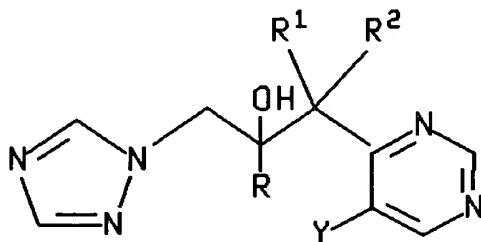
New claims 26 and 27 each cover compounds falling within claim 1 except each recites a more narrow genus. New claim 28 covers the subject matter of original claim 6 which has been amended herein to be slightly broader. New claim 29 covers the compound of claim 8 which has been canceled.

The pending claims have been rejected on two grounds. First, the claims have been rejected under 35 U.S.C. §103 as covering unpatentable subject matter in view of U.S. Patent No. 5,116,844 ("Dickinson") and European Patent Application Publication No. 332,387 ("Oida"). Second, claims 10-19 have been rejected "under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9" of Dickinson. Both rejections are responded to below.

The Claimed Compounds Are Not Obvious Over The Cited References

Oida Does Not Disclose Applicants' Claimed Compounds

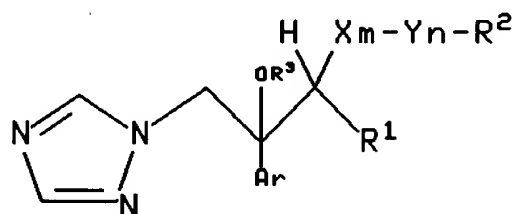
Claim 1, the broadest composition claim under consideration, covers a narrow genus, as follows:



wherein R is phenyl substituted by 1 or 2 substituents each independently selected from halo and -CF<sub>3</sub>; R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl; R<sup>2</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and Y is F or Cl. This specific genus

constitutes a classic "selection" invention where such a specific genus may fall within a general area of compounds disclosed in the art but the specific genus is not specifically referred to or suggested in the art. Applicants disclose that the claimed compounds have an unexpectedly high level of antifungal activity which is primarily attributable to their surprisingly long half-lives ( $t_{1/2}$  values).

Oida refers to an extremely broad range of triazole compounds having fungicidal activity. Oida refers to a generic structure, reproduced below, which encompasses several thousand compounds:

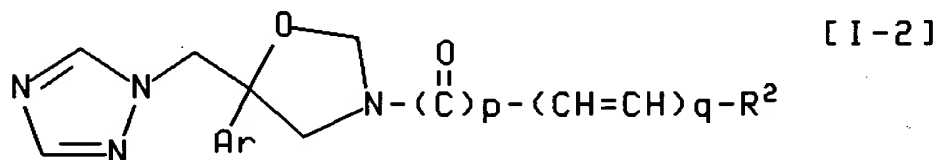
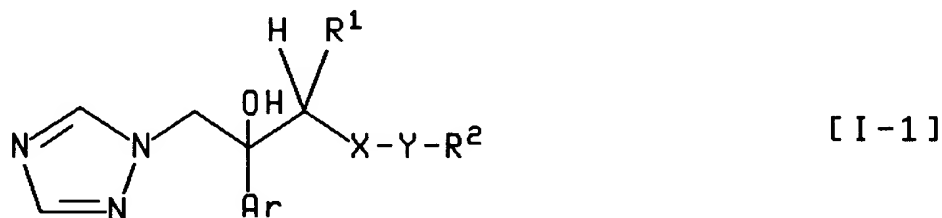


This structure includes 8 variables ( $R^1$ ,  $R^2$ ,  $R^3$ , Ar, X, m, Y, n). Two variables represent integer values (m and n) and the remaining variables encompass a large number of chemical groups. Certain variables, such as Y, can be chemical groups which include further variables such as  $R^4$  and  $R^5$  which also represent a number of chemical groups. Oida provides an extensive list of the different groups and values encompassed by each variable. (See pages 2-3 of Oida)

By conservative estimate, Oida's generic structure encompasses approximately 50,000 compounds. The number grows even higher if you consider "variables within variables" such as  $R^4$  and  $R^5$ . Within Oida's generic and specific discussion,

there is no teaching or suggestion of applicants' claimed compounds.

Oida specifically describes 347 compounds. None of the compounds specifically described by Oida is structurally similar to applicants' claimed compounds. The compounds specifically mentioned by Oida are based on two structures identified as (I-1) and (I-2), reproduced below.



Structure (I-2) is distinctly different from applicants' claimed compounds. The 1-oxa-3-azacyclopentane ring which forms an integral part of structure (I-2) does not come within the scope of any possible R, R<sup>1</sup>, or R<sup>2</sup> substituent in applicants' claimed structure. Further, the 1-oxa-3-azacyclopentane ring of structure (I-2) is not structurally similar to the pyrimidinyl ring in applicants' claimed structure. Thus, applicants' claimed compounds are not *prima facie* obvious in view of Oida et al.'s structure (I-2).

With respect to structure (I-1), the only compounds that bear any relation to applicants' claimed compounds have the following characteristics:

<u>No.</u>	<u>Ar</u>	<u>R<sup>1</sup></u>	<u>R<sup>2</sup> - Y</u>
1-48	2,4-diClPh	Me	(6-Cl-3-Pyr)-CONH-
1-49	2,4-diClPh	Me	(6-Tfm-3-Pyr)-CONH-
1-50	2,4-diFPh	Me	(5-Tfm-2-Pyr)-CONH-
1-100	2,4-diClPh	Me	(6-Tfm-3-Pyr)-CONMe-
1-102	2,4-diClPh	Me	(6-Cl-3-Pyr)-CH=CH-CONMe-
1-143	2,4-FPh	Me	(4-Pyr)-CONH-
1-144	2,4-diFPh	Me	(2-Pyr)-CONH-

The groups are self explanatory with the provision that the terms "Pyr", "Tfm" and "Ph" represent pyridinyl, trifluoromethyl and phenyl groups, respectively.

Applicants' claimed structure is distinctly different. Applicants' claimed compounds include a pyrimidinyl ring rather than a pyridinyl ring. The (I-1) structures above also differ from the claimed compounds by the presence of an amide linkage separating the pyridinyl ring from the remainder of the compound. Applicants' claimed compounds fall under different classifications and are patentably distinct from the specific (I-1) chemical structures referred to by Oida. Thus, applicants' claimed compounds are not *prima facie* obvious in view of the specific compounds referred to by Oida.

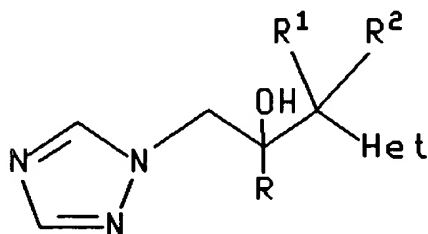
The Examiner states that applicants' claimed compounds are suggested by the generic disclosure of Oida. A generic disclosure, without a specific teaching which suggests

applicants' claimed compounds, cannot sustain a *prima facie* case of obviousness. See In re Jones, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

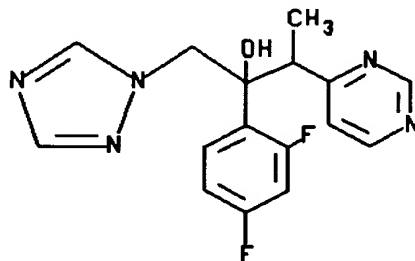
In Jones, the Solicitor contended that, while no specific compound referred to by the cited art was similar to the claimed compounds at issue, the generic structure disclosed by the cited art suggested the claimed compounds because the generic structure encompassed the claimed compounds. Id. The Federal Circuit held that the claimed compounds were not *prima facie* obvious over the cited reference because the compounds specifically referred to by the cited reference were not structurally similar to the claimed compounds at issue. Id. at 1943-44. The Court stated that the "lack of close similarity of structure is not negated by the fact that the claimed [compound] is a member of the [cited reference's] broadly disclosed genus." Id. As in Jones, applicants' claimed compounds are not *prima facie* obvious over Oida because Oida lacks any specific teaching which would suggest applicants' claimed compounds.

The Claimed Compounds Are Patentable Over Dickinson

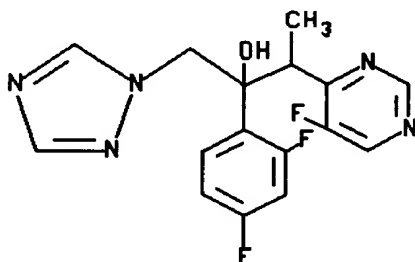
Dickinson discloses triazole antifungal compounds having the following structure:



In this structure, R is a substituted phenyl group, R<sup>1</sup> is a C<sub>1</sub>-C<sub>4</sub> alkyl group, and R<sup>2</sup> is H or a C<sub>1</sub>-C<sub>4</sub> alkyl group. "Het" represents various heterocyclic groups, optionally substituted, including the pyrimidinyl group. Of the various compounds specifically referred to by Dickinson, the following is the closest structurally to applicants' claimed compounds:



Applicants, however, have made a direct comparison of this compound with the closest claimed compound. The claimed compound which is closest structurally to the compound referred to by Dickinson, illustrated above, is the following:



At pages 55-57 of the present application, applicants describe the *in vivo* activity of the Dickinson and claimed compounds against Aspergillus fumigatus infection in mice. European Patent Application No. 89307920.2, which is referred to at pages 55-57 of the application, corresponds in disclosure to Dickinson. At page 57 of the instant application, applicants

establish that, after ten days, 4 out of 5 mice were cured of the induced infection when treated with applicants' claimed compound while no infected mice were cured when treated with the Dickinson compound. The ability of the claimed compounds to quickly and completely rid the mice of infection is a surprising and unexpected advantage.

There is no suggestion in Dickinson of the surprising and unexpected advantage of applicants' claimed compound. This unexpected advantage clearly rebuts the Examiner's case of obviousness. Applicants submit that, in view of this comparative evidence, the compounds of claim 1 are not obvious in view of Dickinson.

Claim 1 has been narrowed. With this amendment, R is phenyl substituted by 1 or 2 halogens or  $-CF_3$ . It is well known that halogens and  $-CF_3$ , as substituents, bear substantially similar pharmacological activity. Given the narrow genus of claim 1, the comparative data submitted is sufficient to establish that the compounds of claim 1 are unexpectedly superior anti-fungal agents than the compounds of Dickinson. See Ex parte Winters, 11 USPQ2d 1387 (BPAI 1989) (one claimed compound compared to art compound sufficient to establish unexpected advantage where claim covers 4 compounds and their salts).

#### Claim 26 Is Patentable Over Dickinson

Applicants submit that claim 26 covers only 2 compounds and their salts. The comparative data that is described on page 57 of the application covers a compound falling within claim 26. In Ex parte Winters, referred to above, the Board



of Patent Appeals and Interferences ruled that comparative data such as that described on page 57 of the present application is sufficient to establish the patentability a claim of such narrow scope. In Ex parte Winters the claim at issue covered 4 compounds and their salts, and this claim was ruled allowable where the applicant compared one compound in the claim with the closest compound from the prior art. Applicants submit that, as in Ex parte Winters, claim 26 is allowable in view of the comparative data provided on page 57 of the application.

Claim 27 Is Patentable Over Dickinson

Applicants submit that claim 27 covers only 5 compounds and their salts. The comparative data that is described on page 57 of the application covers a compound falling within claim 27. In Ex parte Winters, referred to above, the claim at issue covered 4 compounds and their salts, and this claim was ruled allowable where the applicant compared one compound in the claim with the closest compound from the prior art. Applicants submit that, as in Ex parte Winters, claim 27 is allowable in view of the comparative data provided on page 57 of the application.

Claims 28 And 29 Are Patentable Over Dickinson

Applicants submit that claims 28 and 29 are patentable over Dickinson. Claims 28 and 29 specifically recite the compound that is the subject of the comparative data described on page 57 of the present application. The data, as stated above, makes a direct comparison with the closest compound from Dickinson. The compound of claims 28 and 29 is shown to

be superior to the compound from Dickinson. In view of this showing, applicants submit that the compound of claims 28 and 29 is patentable over Dickinson.

The Double Patenting Rejection Should Be Withdrawn

Claims 10-19 have been rejected under the judicially created doctrine of obviousness-type double patenting over Dickinson. The issue is whether the method of those claims would have been obvious over the disclosure of Dickinson.

General Foods Corp. v. Studiengesellschaft Kohle mbH, 23 USPQ2d 1839, 1845 (Fed. Cir. 1992). In deciding the issue, a comparison is made between what is claimed in Dickinson and what applicants claim, without reference to Dickinson's disclosure. Id.

In making the comparison, it is useful to focus on a "tangible embodiment" falling within the scope of the claim. In re Braat, 19 USPQ2d 1289, 1293 (Fed. Cir. 1991). As shown above, in the discussion of Dickinson, applicants have made a direct comparison of a compound falling within the claims of Dickinson with a compound falling within applicants' claims. The compound chosen from Dickinson falls within each of claims 1-9 of Dickinson and is specifically named in claim 7. Further, the compounds chosen from Dickinson and applicants' claims are the closest in structure. Applicants' compound clearly showed an unexpected advantage in antifungal activity over Dickinson's claimed compound. This evidence effectively rebuts the Examiner's double patenting rejection. See D. S. Chisum, Patents, vol. 3, §9.03[3], pp. 9-42 - 9-47 (1994)(copy

enclosed). Thus, applicants respectfully request that the double patenting rejection be withdrawn.

Claims 26-29 Should Not Be Subject To A Double Patenting Rejection

As specifically stated above, claims 26-29 are very narrow in scope. The comparative data described on page 57 of the application provides a showing of unexpected advantage that is commensurate in scope with claims 26-29. In view of this showing, the compounds of claims 26-29 are not obvious over Dickinson. Thus, a double-patenting rejection over Dickinson would not be appropriate for claims 26-29.

CONCLUSION


For the reasons provided above, applicants respectfully submit that the application is now in condition for allowance. If it is determined that further prosecution on the merits is necessary, it is requested that the specific remarks provided above with respect to claims 26-29 be addressed. To facilitate the prosecution of this application and to discuss applicants' position, if necessary, applicants' attorney respectfully requests an in-person interview with the Examiner to resolve any issues that may remain.

Applicants respectfully petition for a three-month extension of time pursuant to 37 CFR §1.136. Please charge deposit account no. 16-1445 the fee required for a three-month extension of time, as set forth in 37 CFR §1.17(c). Since this amendment introduces 4 new independent claims, it is

believed that, pursuant to 37 CFR 1.16(b), a fee is due with the addition of these claims. Please charge deposit account no. 16-1445 the amount required for the addition of claims 26-29. If any other fee is deemed due relating to this amendment, please charge account no. 16-1445 appropriately. A second copy of this Amendment is enclosed.

Date: February 1, 1996

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